Table S1. Summary of Competitive Analysis and Functional Analysis of hCB_1 WT and mutant receptors in the cAMP assay, βarrestin2 assay, and **[^{35}S]-GTPγS binding assay**.

Summary of competitive analysis at hCB_1 in Figure S1.

Agonist	Antagonist	Inhibition of cAMP accumulation	
		K_B (nM)	pA_2
CP55,940	Rimonabant	0.36 ± 0.15	9.52 ± 0.17
	AM6538	1.26 ± 0.61	8.99 ± 0.20
THC	Rimonabant	0.64 ± 0.09	9.20 ± 0.06
	AM6538	0.40 ± 0.07	9.41 ± 0.08
Agonist	**Antagonist**	**βarrestin2**	
		K_B (nM)	pA_2
CP55,940	Rimonabant	0.44 ± 0.20	9.52 ± 0.31
	AM6538	0.68 ± 0.34	9.37 ± 0.35
THC	Rimonabant	2.94 ± 1.35	8.73 ± 0.35
	AM6538	3.09 ± 2.39	7.81 ± 1.35
Agonist	**Antagonist**	**[^{35}S]-GTPγS binding in mouse cerebellum**	
		K_B (nM)	pA_2
CP55,940	Rimonabant	0.096 ± 0.021	10.05 ± 0.11
	AM6538	0.107 ± 0.024	10.00 ± 0.08

Data are presented as mean ± S.E.M., n = 3-4 experiments performed in duplicate. Data were normalized to the maximum stimulation obtained with CP55,940 within each experiment and fit to a competitive nonlinear regression model using GraphPad 6.0 wherein the Schild slope was constrained to unity.

Functional Analysis of hCB_1 mutant receptors in the cAMP accumulation assays in Figure S5.

	CP55,940 EC_{50}, nM			IC_{50}[a], nM	
hCB_1R	CP55,940	+ 1 μM Rimonabant	+ 1 μM AM6538	Rimonabant	AM6538
WT	5 ± 2	1363 ± 209	1148 ± 383	102 ± 21	84 ± 17
F170W	13 ± 2	765 ± 119	1200 ± 335	163 ± 26	76 ± 10
F170A	18 ± 4	15 ± 2	10 ± 1	NC	NC
F174W	16 ± 6	748 ± 48	1211 ± 405	122 ± 2	61 ±17
F174A	9 ± 2	10 ± 2	8 ± 2	NC	NC
F379W	37 ± 14	—	—	59 ± 16	19 ± 14
F379A	2278 +193	—	—	74 ± 13	35 ± 10

[a] IC_{50} values determined relative to % CP55,940 dose stimulation as indicated in Figure S4. NC: not converged to nonlinear regression; —: not determined. Data are presented as mean ± S.E.M., n = 3-5 experiments performed in duplicate.